REMARKS

Claims 1-3, 5, 6, 9-12, 24 and 25 are pending. Claims 13-23 have been cancelled as drawn to a nonelected invention. Claims 1 and 2 have been amended. The amendments to claims 1 and 2 are supported by disclosure at page 2, lines 19-21 of the specification. No new matter has been added.

35 U.S.C. § 112, first paragraph

Claims 1-3, 5, 6, 9-12, 24, and 25 were rejected for lack of enablement. The Examiner's grounds for rejection appear to be based on the position that "neither the specification nor the prior art taught any such nucleic acids that upon administration to a mammal, as claimed, would have the claimed functions of inhibiting formation of an atherosclerotic lesion." Office Action dated May 6, 2003 at page 5, lines 6-9. The Examiner has cited several references to support the enablement rejection in order to emphasize that:

> . . . while design of antisense for use in cells in cell culture is possible for a known target gene, there is a high level of unpredictability in the art for making and using antisense in whole organisms and further where treatment effects might be obtained. There is no specific guidance in either the specification as filed or the prior art to provide one of skill in the art the information needed to overcome the unpredictability in the art cited in the previous Office action.

In particular, the Examiner argues that Applicants failed to address the points raised in the cited references with regard to the antisense art.

> Those references clearly stated that there is not a known optimization of antisense that will allow antisense to predictably work in a whole organism since antisense functions differently *in vivo* than *in vitro*. As noted in the previous Office action, antisense to one target gene does not allow the determination of the effects of antisense to another target gene. Furthermore, there are numerous examples of attempts to use antisense to a particular target gene *in vivo*, where there was no success since the right concentration could not be achieved, the antisense was

toxic, had too much non-specific binding, or was degraded too quickly prior to location of its target *in vivo*.

Claims 1-3, 5, 6, and 9-12 are directed to methods of inhibiting formation of an atherosclerotic lesion by contacting a macrophage with an inhibitor of AFABP expression and methods of inhibiting differentiation of a macrophage into a foam cell by administering antisense oligonucleotides. Claims 24 and 25 are directed to methods of inhibiting differentiation of a macrophage into a foam cell and methods of inhibiting formation of an atherosclerotic lesion by reducing the expression of AFABP by administering a non-nucleic acid compound that binds to a cis-acting regulatory sequence of AFABP.

"Prior to the invention, it was thought that AFABP expression was limited to adipocytes." Specification at page 11, lines 1-2. Applicants made a significant contribution to the field of cardiovascular medicine by showing that "AFABP was found to be expressed in macrophages and macrophage-derived foam cells associated with atherosclerotic lesions (but not circulating monocytes)." Specification at page 11, lines 3-5. Applicants elucidated a molecular mechanism by which atherosclerotic lesions develop by presenting data, which demonstrates that atherosclerotic lesions from hypercholesterolemic, apolipoprotein E deficient (ApoE-/-) mice (but not arterial walls from normal mice) contain high levels of AFABP mRNA. *See* Specification at page 21, line 4 through page 23, line 6. The inventors teach that the effect of decreasing AFABP is to inhibit the formation of atherosclerotic lesions, even in the presence of high cholesterol as in the example of the ApoE-/- mouse. *See* Specification at page 24, line 1 through page 26, line 2. Therefore, Applicants submit that the claims are commensurate with their contribution to the field.

The specification provides ample direction to enable one skilled in the art to practice the invention as claimed. For example, the target gene, AFABP, is identified and the murine and

human sequences are provided in the specification as SEQ ID NO:1 and SEQ ID NO:2, respectively. Moreover, the specification provides guidance regarding the regulation of AFABP expression for example, the AFABP enhancer sequence is disclosed as SEQ ID NO:8. *See* Specification at page 15, lines 15-29. Most significantly, the specification teaches that an "antisense nucleic acid to be administered has the sequence of the complement of SEQ ID NO:6." Specification at page 9, lines 6-7; SEQ ID NO:6 sequence disclosed at page 6, lines 7-11. Thus, Applicants contend that the claims are commensurate with the scope of the disclosure.

One reasonably skilled in the art could make and use the invention from the disclosures in the application coupled with information known in the art without undue experimentation. With respect to making the antisense oligonucleotides, Applicants have provided the target sequence and an antisense sequence (*i.e.*, the complement of SEQ ID NO:6). Antisense oligonucleotides based on the disclosed sequences are generated by methods well known in the art, including standard chemical synthesis, ligation of constituent oligonucleotides, and transcription of DNA complementary to the coding sequence. *See* Specification at page 10, lines 27-30. Methods to increase antisense oligonucleotide stability are also discussed. For example incorporating 3'-deoxythymidine or 2'-substituted nucleotides, providing the oligonucleotides as phenylisourea derivatives, or linking aminoacridine or poly-lysine to the 3' ends of the oligonucleotides serve to increase antisense oligonucleotide half-life *in vivo*. *See* Specification at page 10, lines 13-30. With respect to using the antisense oligonucleotides, a macrophage-specific promoter, scavenger receptor A gene promoter, is disclosed, as well as appropriate vectors for use in antisense treatment. *See* Specification at page 9, line 8 through page 10, line 6. Delivery systems, such as liposomes, receptor-mediated delivery systems, non-viral nucleic acid-based vectors, erythrocyte ghosts, and microparticles, are disclosed in the specification at page

10, lines 6-12, and are well-known and used in the art. Modes of administering non-nucleic acid inhibitors of AFABP expression are disclosed at page 13, line 5 to page 14, line 20 of the specification. Such transcription inhibitors, peroxisome proliferator-activated receptor gamma (PPARγ) and peroxisome proliferator-activated receptor alpha (PPARα), and their mechanism of action are disclosed at page 1, line 20 to page 2, line 5 and page 21, lines 4-21 of the specification. Therefore, one skilled in the art of antisense could make and use the invention as claimed.

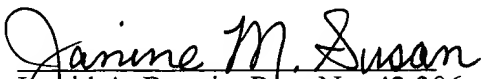
The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. As discussed above, degradation is addressed in the specification as the Applicants provide ways to stabilize the antisense oligonucleotides. Applicants also provide an assay, namely the differentiation of macrophages into foam cells, which can be used to measure effective concentration and specificity of antisense oligonucleotides. These assays and the art-recognized mouse model disclosed in the specification, coupled with the knowledge of those skilled in the art of gene expression technology, enables the determination of effective concentration, specificity, and toxicity of antisense oligonucleotides suitable for the inhibition of macrophages into foam cells and the resultant formation of atherosclerotic lesions. Therefore, Applicants submit that they have provided adequate guidance for determining the factors presented in the cited references, *i.e.* concentration, toxicity, specificity of binding, and rate of degradation. Moreover, this is the type of experimentation that those skilled in the art routinely perform.

Applicants submit that with the specification in hand, one skilled in the art would be able to practice the invention as claimed. Withdrawal of the rejections under §112 is respectfully requested.

CONCLUSION

On the basis of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,



Ingrid A. Beattie, Reg. No. 42,306
Janine M. Susan, Reg. No. 46,119
Attorneys for Applicants
c/o MINTZ, LEVIN, COHN, FERRIS, GLOVSKY & POPEO, P.C.
One Financial Center
Boston, Massachusetts 02111
Tel: (617) 542-6000
Fax: (617) 542-2241

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